2. SYNOPSIS

Study centre(s)

The study was performed at 9 study centres located in different regions of India.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Outcome

Objectives	Outcome Measure:
Primary To describe the adverse even s profile of dapagliflozin + saxagliptin fixed dose combination in Indian Type 2 Diabetes Mellitus (T2DM) patients at 24 weeks	• Adverse Events (AEs) including SeriousAdverse Events (SAEs), AEs leading to Discontinuation (DAE), and adverse events of special interest (volume depletion, renal events, major hypoglycemic events, fractures, urinary/genital tract infections,diabetic ketoacidosis, amputations, and hospitalization for heart failure) • Safety laboratory values • Electrocardiogram (ECG) • Vital Signs (pulse and BP) • Physical examination
Secondary To describe the efficacy of dapagliflozin + saxagliptin fixed dose combination in Indian T2DM patients at 24 weeks	• HbA1c change at week 24 compared to baseline. • Weight change at week 24 compared to baseline. • Syst lic Blood Pressure (SBP) change at week 24 compared to baseline. • Fasting Plasma Glucose (FPG) change at week 24 compared to ba eline

Study design

This was a prospective, multicenter, phase IV study to assess the safety of fixed dose combination (FDC) of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2DM) patients. The study was initiated after approval by the Ethics Committee and was conducted at 9 different study centres in India that enrolled T2DM patients.

204 patients underwent the screening phase prior to receiving the first fixed dose of dapagliflozin and saxagliptin combination. Patients who met the protocol-defined inclusion/exclusion criteria were enrolled in the study. The subjects participating in the study underwent following phases: Screening/Enrolment Phase, Treatment Phase, and Follow-up Phase (after End of Study (EOS)).

Target population and sample size

The total sample size of the study was 204 (Indian patients with T2DM). The primary endpoint of the study was to assess the safety of FDC of dapagliflozin and saxagliptin in these patients.

Eligible patients who met the following inclusion and exclusion criteria were included in the study:

Inclusion criteria

1) Male and female patients aged > 18 and above.
2) Documented history of T2DM with HbA1c level >7.0% and ≤ 10% at the screening visit.
3) Patients who were on a stable dose of anti-diabetic drugs (including Metformin dose between 1000-2000 mg) in the past 3 months.

Exclusion criteria

1) Known allergies or contraindications to the contents of the Investigational product (IP), dapagliflozin or, saxagliptin tablets.
2) Type 1 diabetes mellitus.
3) Treatment with a SGLT2 inhibitor, GLP-1 agonist or DPP4 inhibitors at Visit 1 or 2.
4) Patients with moderate to severe renal impairment (eGFR persistently <45 mL/min/1.73 m2 by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula or end-stage renal disease (ESRD)) or unstable or rapidly progressing renal disease.
5) Patients with severe hepatic impairment (Child-Pugh class C).
6) History of pancreatitis or pancreatic surgery.
7) Patients with a history of any malignancy.
8) Patients with any of the following CV/Vascular Diseases within 3 months prior to signing the consent at enrolment, as assessed by the investigator:
    - Myocardial infarction.
    - Cardiac surgery or revascularization (CABG/PTCA).
    - Unstable angina.
    - Transient ischemic attack (TIA) or significant cerebrovascular disease.
    - Unstable or previously undiagnosed arrhythmia.
9) History of heart failure.
10) Severe uncontrolled hypertension defined as systolic blood pressure≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg at any visit up to randomisation.
11) History of diabetic ketoacidosis.
12) Any acute/chronic systemic infections.
13) Recurrent urogenital infections.
14) Patients at risk for volume depletion as judged by the investigator.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

Patients were given once-daily FDC of Dapagliflozin 10 mg / Saxagliptin 5 mg orally at the same time of the day throughout the study for 24 weeks, or until study drug was discontinued, due to either voluntary discontinuation, risk to subject as judged by the investigator, AEs, or major and/or frequent hypoglycemic events, or other reasons, whichever occurred earlier. Every attempt was made to ensure that the patients remained on the designated therapy for the entire 24-week study duration.

Other Medicinal products:

Patients were allowed to continue receiving medicines other than the study drug, as per investigator's discretion. Patients were eligible to receive additional glucose lowering drugs if they met the rescue criteria, as per the details provided in the rescue therapy section. The sponsor did not provide any other medicine except for the IP, Dapagliflozin 10 mg / Saxagliptin 5 mg.

Duration of treatment

The duration of treatment was 24 weeks or until study drug discontinuation due to either voluntary discontinuation, risk to the subject as judged by the investigator, AEs, or major and/or frequent hypoglycemic events, or other reasons, whichever occurred earlier.

Statistical methods

This study was conducted to fulfil the regulatory requirements in India. The objective was to establish that the FDC of Dapagliflozin 10 mg / Saxagliptin 5 mg is a safe treatment option in Indian patients with T2DM. This study was planned as a prospective study on 200 patients in single-arm open-label study. CCI [redacted]

Data was summarized using descriptive statistics. Continuous variables were summarized using the number of observations, mean, standard deviation (SD), median, and range as appropriate. Categorical values were summarized using the number of observations and percentages as appropriate.

The safety analysis population included all patients who had signed the ICF and had received at least one dose of study medication. The safety analysis population was also applicable to the efficacy analysis, and any efficacy measurements collected before the study medication discontinuation were included.

Any AE that occurred within 2 weeks of discontinuation of IP (i.e., the last dose of study medication) was included in the AE summaries. Any event in this period that occurred after a patient received further therapy (following discontinuation of the study drug) were flagged in the

data listings. The mean change in HbA1C from baseline to 6 months for patients was analysed using paired t-test / Wilcoxon signed-rank test at a 5% level of significance.

The study was designed in accordance with the Health Authority requirements in India. It was intended to provide information regarding the safety profile for patients in India, and to provide additional information to the overall safety profile of Dapagliflozin/ Saxagliptin FDC. Due to the small sample size, this study was not directly compared to the data from any other country.

Study population

A total of 204 T2DM patients were screened across 9 different study centres in India. 196 patients passed the screening after meeting all the inclusion and exclusion criteria. They were selected and were enrolled in the study. These 196 patients received the FDC of Dapagliflozin 10 mg / Saxagliptin 5 mg. All the enrolled patients were Asian, and the majority of which were males [120 (61.2%)]. The median age of patients was 53.0 years (ranging from 20 to 78 years). The mean height of all patients was 163 cm, with a mean weight and body mass index (BMI) of 74.2 kg and 28 Kg/m^2, respectively. The mean HbA1C, FPG, and BP of all patients were reported to be 8.6%, 162 mg/dl, and 126 mmHg respectively.

Summary of safety results

Treatment with FDC of dapagliflozin and saxagliptin in Indian T2DM patients for 24 weeks showed that there were no new safety signals.

Of the 196 patients, a total of 22 (11.22%) patients experienced 40 AEs. All AEs were treatment emergent. The majority of AEs were judged by the investigator as not related to the study drug (13[6.63%] patients). AEs were categorized according to severity as mild, moderate, and severe. The majority of AEs were mild (20 [10.20%] patients) and 5 (2.55%) patients experienced moderate AEs. No SAEs, deaths or AEs leading to discontinuation (DAEs) were reported during the study. 18 (9.18%) patients with AEs required drug treatment whereas 2 (1.02%) patients were given non-drug treatment. The study drug was temporarily interrupted in 3 (1.53%) patients due to AEs. The outcome of AEs was categorized as recovered without sequelae, recovered with sequelae, recovering/resolving, not recovered, unknown, and fatal. A total of 20 (10.22%) patients recovered without sequelae whereas 4 (2.04%) patients were recovering/resolving.

Overall, the most frequently reported AEs by system organ class were infections and infestations (9[4.59%] patients), followed by general disorders & administration site conditions (5[2.55%] patients) and gastrointestinal disorders (4[2.04%] patients). Urinary tract infection, pyrexia, nasopharyngitis, balanoposthitis, nausea, and vomiting were the more frequent AEs experienced by these patients. The AEs of special interest included genital tract infection (3[1.53%] patients) and hypoglycemic events (1[0.51%] patient). No SAEs or deaths were reported during the study.

No clinically significant findings were observed amongst the haematology parameters, clinical chemistry parameters, and urinalysis. Further, no clinically significant abnormalities in physical examinations, vital signs, and ECG were reported during the treatment period.

Summary of efficacy results

The efficacy of the FDC of Dapagliflozin + Saxagliptin in Indian T2DM patients was analysed by measuring the changes in HbA1c, weight, Systolic Blood Pressure (SBP), and Fasting Plasma Glucose (FPG) at Week 24, compared to baseline.

In this study, mean change (SD) [95% CI] from baseline in HbA1c after 24 weeks of treatment was -1.2 (1.09) [-1.34, -1.03]. The change in HbA1c from baseline to Week 24 was statistically significant ($p<0.0001$).

Further, the mean change (SD) [95% CI] in weight from baseline to Week 24 was -2.1 (3.98) [-2.66, -1.51]. The change in weight was statistically significant ($p<0.0001$).

After 24 weeks of treatment with dapagliflozin + saxagliptin, the mean change (SD) from baseline in SBP was -0.2 (12.90) [-2.34, 1.91]; but the difference was not statistically significant ($p=0.8416$).

The mean change (SD) in FPG from baseline after 24 weeks of treatment was -24.4 (62.89) [-33.4, -15.4]. An overall reduction in FPG was observed from baseline to week 24 ($p<0.0001$).

Conclusion(s)

- In conclusion, no new safety concerns were reported in this study with FDC of dapagliflozin + saxagliptin in Indian T2DM patients. All the AEs reported during the study were treatment emergent and were mild or moderate in nature, with majority of them being mild in severity. No deaths, SAEs, or other significant AEs were reported in the study. Moreover, majority of the AEs were judged as not related to the study drug by the investigators. Urinary tract infection, pyrexia, nasopharyngitis, balanoposthitis, nausea, and vomiting were the more frequently reported AEs experienced by the patients. The AEs of special interest included genital tract infection and hypoglycemic events which were seen in the miniscule number of patients during the study.

  No clinically significant findings were observed amongst haematology parameters, clinical chemistry parameters, urinalysis, physical examination, vital signs, and ECG during the treatment period.

- In terms of efficacy, the study showed that there was a statistically significant decrease in HbA1c from baseline after 24 weeks of treatment. This indicates that the dapagliflozin + saxagliptin, a fixed dose combination is effective in Indian patients with T2DM.

- Further, the reduction in body weight from baseline to Week 24 was also found to be statistically significant.

- Also, statistically significant reduction in FPG from baseline to Week 24 was reported indicating that the combination has a beneficial effect in controlling FPG in Indian patients with T2DM.
- Lastly, after 24 weeks of treatment with the combination of dapagliflozin + saxagliptin, there was a small mean reduction in SBP when compared to the baseline. However, the difference was not statistically significant.

Thus, dapagliflozin + saxagliptin combination once daily was found to be effective, safe, and well-tolerated in adult Indian patients with T2DM. The efficacy and safety profile support a positive benefit versus risk profile of dapagliflozin + saxagliptin FDC in the T2DM adult population which is line with the global clinical development program.